MYASTHENIA GRAVIS

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Definition

MYASTHENIA GRAVIS is a disorder of neuromuscular conduction. It is characterised clinically by an excessive degree of weakness which develops in the affected muscles during sustained or repeated contraction. In the early stages of the illness, at least, the strength is partially or fully restored by rest or the administration of anticholinesterase drugs in the appropriate dosage.

Natural History

Incidence and age at onset

The incidence of the disease in the total population has been estimated between 1 in 40,000 (Garland and Clark, 1956) and 1 in 15 to 20,000 (Eaton, 1958), and it is found more commonly in women, in a proportion 3 to 2 (Schwab and Leland, 1953; Ferguson, Hutchinson and Liversedge, 1955).

Although myasthenia gravis may develop at any age, in either sex, it occurs most commonly between the ages of 15 and 65 years. The majority of new cases in women appears during reproductive life so that the mean age of onset is 26 years. In men the distribution curve is more symmetrical and the mean age of onset is 31 years (Simpson, 1958). The relationship of myasthenia gravis to pregnancy and the menstrual cycle is considered below.

Progressive myasthenia gravis may occur in childhood, and a rare, transient form, neonatal myasthenia is sometimes found in the children born to women with myasthenia.

Family History

Several authors have recorded the multiple incidence of myasthenia gravis in one family (Oppenheim, 1898; Rothbart, 1937; Teng and Osserman, 1956), but on present evidence this cannot be considered as a familial disease (Simpson, 1964). However, a careful scrutiny of the family histories of patients with myasthenia gravis reveals an unusual incidence of thyroid disease and rheumatoid arthritis. In common with myasthenia gravis, an auto-

immune mechanism has been postulated as an aetiological factor in the causation of these disorders and it may be that the myasthenic patient is genetically predisposed to his disease (Simpson, 1960).

Onset

The onset of the disease is commonly insidious, and may at first be neglected by the patient. In such circumstances it is difficult to establish any precipitating factor. In a large number of cases, however, the first recognised symptoms come on with dramatic suddenness. In such a case the precipitating factor is more readily identified. This can be a physical or emotional shock, and one may be tempted to diagnose hysteria, particularly if the patient is examined after a period of rest when the symptoms and signs have disappeared. The stress associated with injury and infection, particularly lobar pneumonia, has been related to the onset of myasthenia gravis. The first symptom may appear in the early months of pregnancy, or during the puerperium. In an established case, sudden worsening may appear to be precipitated by similar circumstances.

The disease may first be recognised by the patient's abnormal response to drugs. The patient with myasthenia gravis is especially sensitive to curare and there may be a failure to establish normal respiration after surgery when muscle relaxants have been used. There is uncertainty about the role of procaine as a precipitant. I examined an elderly woman with ocular myasthenia, whose first symptoms developed after an operation for cataract, performed under procaine anaesthesia.

Course of the disease

The susceptibility of the affected muscles to rapidly increasing weakness or "fatigue" has already been stressed. Unlike normal fatigue myasthenic "fatigue" proceeds to complete paralysis. Most patients feel stronger in the morning and fatigue more readily in the

FIG. 1.—Percentages of cases in which various muscle groups are affected at the onset (left of key) and at some time during the illness (right of key). Simpson, J. A. (1960). *Scot. Med. J.*, 5, 419.

afternoon or evening. Paradoxically, some patients feel at their worst in the morning improving as the day goes on. A comparable situation exists in that some patients feel that they can “work off” incipient weakness by active effort. Apart from physical effort there are environmental factors which influence the course of the illness. Extremes of temperature cause an increase in weakness: the very local increase in temperature experienced in a hot bath may exaggerate the weakness. One or two patients have described a worsening of ocular symptoms in bright sunshine perhaps provoked by actively screwing up their eyes.

Reference has been made to the higher incidence of myasthenia gravis in women of reproductive age and the fluctuations experienced during pregnancy and the puerperium. The likelihood of deterioration is greatest during the first trimester of pregnancy, with

some improvement during the later months (Viets, Schwab and Brazier, 1942). Relapse may occur during the puerperium (Fraser and Turner, 1953). There is often a transient premenstrual worsening, but it is uncertain whether this represents a true physical impairment. Objective evidence of a disturbance associated with menstruation seemed to be provided by Schrire (1959) who described a reduction in the excretion of pregnandiol by non-pregnant myasthenic women, but Simpson (1964) was unable to confirm these findings.

The patient’s emotional state plays a great part in determining his response. Enthusiasm and confidence in the patient and the attending physician auger well in the management of the disease.

While minor fluctuations in the severity of the disease are common, complete remission is relatively rare. The most marked variations in

severity occur within the first seven years of the illness and the risk of death, directly attributable to the myasthenic process is also greatest during this period. By the same token any worthwhile remission is more likely to occur during the first seven years. It is rare for a patient to have more than one complete remission.

After seven years, dramatic changes in the state of the disease are uncommon and it is then said to have become stabilised. Thymectomy as a treatment for myasthenia gravis is most likely to be effective if undertaken during the pre-stable period (Simpson 1958, 1960).

Distribution of the affected muscles

Myasthenia gravis may affect any voluntary muscle in the body: the smooth muscles are not affected. It is unusual for all the muscles to be affected at any one time. Characteristically, some muscles are severely affected, some more slightly, and some not at all. By summarising the extent of the disease in a large number of patients it is possible to construct a statistical distribution of the affected muscles (Fig. 1 (Simpson, 1960)).

The muscles around the eyes, the extra-ocular muscles, the levators of the upper lids and the orbiculares oculi, are most often found to be involved. Indeed it is uncommon for a patient with myasthenia gravis to have no symptoms or signs referable to these muscles. A too rigid adherence to this statement, however, will result in some atypical cases remaining undiagnosed.

The muscles of the face, tongue, jaw and palate, and pharynx are almost as frequently affected as those around the eyes. These are followed by the muscles of the neck, shoulders and pelvic girdle. The peripheral limb muscles, muscles of the trunk and respiration are less commonly involved.

Not infrequently the disease appears to be limited to one group of muscles, and may become static. This occurs most commonly in the muscles around the eyes, and it has prompted some physicians to regard "ocular myasthenia" as a separate entity (Grob, 1953). Careful diagnostic techniques, clinical, pharmacological and electromyographic, will often reveal a more widespread involvement.

In contrast to this static phase, there may be surprisingly rapid changes in the distribution of affected muscles. This is seen most strikingly in the involvement of the levators of the upper eyelids. The patient may describe how he had a unilateral fixed or fatiguable ptosis, when quite suddenly, the affected eye opened and the other eyelid promptly began to droop.

Permanent "myopathic" changes may develop in affected muscles. Simpson recorded myopathic changes in 10% of the females and 20% of the males in his series (Simpson, 1958). These changes are most commonly found in the extra-ocular muscles, the triceps brachii, iliopsoas, quadriceps femoris and the tongue. Such changes are uncommon in muscles which have been affected for only a short time. The duration of weakness is not the only factor, however, as muscles which have been affected for many years may never show myopathic responses. When assessing the patient's reaction to anticholinesterase drugs, the possibility of permanent changes must be considered so that a localised failure of response is not necessarily interpreted as a negative result.

Clinical features

The most outstanding symptom is the development of unusual weakness after a short period of effort.

Involvement of the extra-ocular muscles gives rise to diplopia, which may increase gradually or may develop suddenly so that objects appear to split or slip to one side. Such symptoms may occur while the patient is concentrating on close, fine work, and will often be relieved by closing the eyes for a few moments or looking away to a more distant object. When examining eye movements, the patient's ability to maintain his gaze should be tested. During this examination an increasing strabismus may develop and nystagmoid jerks are commonly seen. These represent the development of weakness, with a recovery of strength after a momentary rest.

Unilateral ptosis may relieve the patient of his diplopia. Ptosis may be seen to develop during the examination and minimal degrees of ptosis are sometimes compensated by overaction of the frontalis muscle on that side (Fig. 2). The patient may be unable to close his eyes tightly, due to weakness of the orbiculares oculi. He may then complain that soap gets into his eyes when he washes his face. When he closes his eyes tightly, the eyelashes which are normally buried in the folds of skin, remain visible. The eyelids may also be prised apart with unusual ease.

Weakness of the muscles of mastication becomes most prominent during a meal. The patient often complains that he has difficulty in chewing meat. As with the other symptoms, he can usually start chewing with no difficulty but as the meal progresses the weakness increases. Involvement of the facial muscles and

FIG. 2.—Patient with florid myasthenia gravis.

FIG. 3.—Improvement during the edrophonium test.

tongue adds to the difficulty in eating and clearing the mouth. A fatiguable dysphagia is a common complication, and weakness of the soft palate results in the nasal regurgitation of fluids. Dysphagia may be demonstrated by the fluoroscopic screening of a barium swallow (Viets, 1947). The barium remains pooled in the pyriform fossa, and the injection of an anticholinesterase drug will then restore normal passage down the oesophagus. Facial weakness may let the lips droop open and allow saliva to dribble from the mouth. Attempts to smile result in the characteristic snarl (Fig. 4). It may be difficult for the patient to protrude his tongue, and selective involvement of the lingual muscles causes a triple groove appearance. This grooving can often be abolished by adequate medication, but myopathic changes may make it irreversible. "Bulbar weakness" such as described in this paragraph, also gives rise to a peculiar thickening of the speech and fading of the voice.

The extensor muscles of the neck are usually more severely affected than the flexors and the patient with florid myasthenia gravis can often be recognised, supporting his head and jaw on his hand (Fig. 2).

Involvement of the muscles of the shoulder girdle is only apparent when the patient is obliged to raise his arms above his head. Women may find that routine hair-dressing causes extreme fatigue: similarly, hanging up washing on a clothes-line can first bring this symptom to notice. Pelvic girdle weakness

FIG. 4.—The myasthenic "snarl".

gives rise to difficulty in climbing stairs, or impairs the stability of the hip, so that the patient walks with a waddling gait or falls due to sudden weakness of the glutei.

It is relatively uncommon for the respiratory muscles to be affected, but when they are, this presents a serious problem of management. Exercise tolerance is severely limited, and failure of the respiratory musculature is apparent in the fading voice, and the rapid, shallow respiration. While the respiratory

excursion may be sufficient for normal breathing, the cough is often too weak to clear accumulated mucus or inhaled food particles.

In contrast to the striking muscular weakness, the tendon reflexes are retained and are sometimes unusually brisk. If the associated muscles are affected by the disease, the tendon jerk will also show progressive fatiguability if it is elicited repeatedly. The plantar responses are always flexor. A widespread absence of tendon reflexes in a patient who exhibits myasthenic fatiguability should suggest a diagnosis of symptomatic myasthenia (see below). A diminished tricep jerk is not uncommonly found and is the result of myopathic changes in that muscle.

It is most unusual to find objective evidence of sensory change. Osserman, Kornfeld, Cohen, Lentins, Mendelow, Goldberg, Windsley and Laplan (1958) described sensory symptoms in 14% of the cases in their series. Symptoms such as aching in neck and shoulders, and headache, may be due to abnormal posture and tension on pain-sensitive structures due to weakness of the muscles. Tingling paræsthesiae in the hands have been ascribed to compression of the brachial plexus resulting from a dropped shoulder syndrome. Some sensory disorders such as anosmia (Alajouanine, Castaigne, Niek, Contamin and Lhermitte, 1957) and ageusia may indicate a direct involvement of sensory fibres (Simpson, 1964).

Relationship with other diseases

Hyperthyroidism has been recognised in as many as 5% of all patients with myasthenia gravis (Millikan and Haines, 1953). Simpson (1958) who included all forms of thyroid disorder found an incidence of 18% in females and 9% in males. Osserman and others (1958), Simpson (1960) and Storm-Mathisen (1961) have published large series of cases recording the occurrence of other diseases, notably rheumatoid arthritis, systemic lupus erythematosus, anaemia, epilepsy and psychotic disorders. The occurrence of these conditions may well be coincidental, but Simpson (1964) insists that significant correlations will be established only if the attending physicians adopt a more open-minded approach to the collection of case material.

Neonatal myasthenia

A transient form of myasthenia in babies born to women with myasthenia gravis was first recognised and treated by Strickroot, Schaeffer and Bergo (1942) and in 1960 Greer

and Schotland summarised the 20 cases reported in the literature up to that time. Millichamp and Dodge (1960) added a further 10 cases. In this form of the disease there is a generalised involvement of all the voluntary musculature, although the ocular signs which dominate the adult symptomatology may not be so apparent. The child has a feeble cry, breathes with difficulty, can scarcely feed and lies limp in his cradle. The response to anticholinesterase medication is dramatic. The symptoms resolve within 2 to 10 weeks after which the child flourishes without medication. It appears that there is a transplacental leak of some unknown humoral substance, from the mother to the child, which interferes with neuromuscular conduction, but does not cause permanent damage to the motor end plate.

Myasthenic reactions in the myopathies

Polymyositis, dermatomyositis and carcinomatous myopathy may simulate myasthenia gravis clinically, pharmacologically and electromyographically (Benedek, 1944; Christensen and Levison, 1950; Ragan, 1950; Eaton and Lambert, 1957; Walton and Adams, 1958; Brain and Henson, 1958). There may be an abnormal fatiguability of the affected muscles, and at first some response to the administration of anticholinesterase drugs. The distribution of the affected muscles is unlike that of myasthenia gravis in that the muscles around the eyes, and the bulbar muscles are usually spared, while the proximal limb muscles bear the brunt of the disease. In contrast to true myasthenia gravis the tendon reflexes are diminished or absent in the myasthenic syndrome and the initial response to anticholinesterase drugs is soon lost.

Pathology

The thymus

The thymus is abnormal in the majority of patients with myasthenia gravis. It may be of normal size or hypertrophied, and shows extensive lymphoid hyperplasia throughout its structure. Numerous germinal centres are seen in the medulla (Castleman and Norris, 1949). A thymic tumour (thymoma) is found in 10 to 20% of all cases. Myasthenia gravis associated with thymoma develops later in life and is more common in men. The medical control of symptoms is often difficult and the results of surgery are frequently disappointing. The tumour is usually benign and may show cyst formation and calcification. Most frequently the tumour lies in the anterior

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mediastinum and can be recognised on plain X-rays of the chest. Both P.A. and lateral views should be obtained. The thymoma is occasionally malignant invading the mediastinal structures and the local lymph glands.

Pathology of nerve and muscle

Although attention has been focused on the neuromuscular junction as the site of the disorder, pathological changes are also found in the motor nerves and the muscle.

Coërs and Woolf (1954, 1959), using a supravital methylene blue stain and a supplementary stain for cholinesterase, showed two distinctive abnormalities in the structure of the nerves from patients with myasthenia gravis. One they called the "dystrophic type" in which there were increased branchings of the terminal nerve arborisation. In the other, the "dysplastic type", the terminal knobs were reduced in number and arranged along elongated motor end plates. The relationship of these changes to the myasthenic defect is the subject of controversy. Bickerstaff and Woolf (1960) regard them as evidence of a coincident process of degeneration and repair and not necessarily the primary disorder. However, MacDermot (1960) described these changes in what were clinically and electromyographically unaffected tissues.

Accumulations of mononuclear cells and lymphocytes in the perivascular spaces known as lymphorrhages are commonly found in the muscles of patients with myasthenia gravis. Their distribution bears little apparent relationship to the distribution of clinically affected muscles. Furthermore such changes are commonly found in other disorders. Russell (1953) classified the muscle changes in myasthenia gravis in three groups:

- Type I — an acute coagulative necrosis of muscle fibres
- Type II — the lymphorrhage
- Type III — focal non-inflammatory swelling of the muscle fibre.

It should be noted that she did not consider any of these changes to be specific for myasthenia gravis.

Pathophysiology

The transmission of the motor impulse across the neuromuscular junction in the normal subject comprises the following sequence of events. The impulse having travelled down the motor nerve arrives at the axon terminal. Its depolarisation is accompanied by the discharge of acetylcholine from submicroscopic

vesicles near the nerve ending. The acetylcholine diffuses across the junction to the membrane of the motor end-plate. Here the molecules of acetylcholine key into the receptor protein. This results in an alteration of the permeability of the motor end-plate so that sodium ions diffuse into the cell and an area of local depolarisation occurs—the end-plate potential. If the end-plate potential is sufficiently large it will initiate a self-propagating wave of depolarisation which spreads across the muscle membrane—the muscle action potential, and the contractile elements of the muscle fibre shorten. The restitution of the ionic constituents of the muscle cell is achieved by a pump mechanism and the cell is then repolarised. Under normal circumstances the acetylcholine is rapidly hydrolysed by the enzyme cholinesterase which is present in the region of the end plates. If acetylcholine persists at the receptor site the normal refractoriness of the junction is prolonged. This is conventionally called a depolarisation block, although the end-plate membrane is in fact repolarised (Thesleff, 1955; Katz and Thesleff, 1957). A disorder of this sequence of events results in delay or interruption of the conduction of the impulse across the junction and is known as *neuromuscular block*.

A refined electrophysiological technique for the investigation of neuromuscular conduction was described by Harvey and Masland (1941) and a more complete account together with the results of a series of pharmacological experiments was given by Grob, Johns and Harvey (1956). These "studies in neuromuscular function" were performed on normal subjects and patients with myasthenia gravis. The results obtained in the patients with generalised myasthenia gravis are summarised briefly—

1. The amplitude of the muscle action potential evoked by a single supramaximal nerve stimulus was lower than that in the normal subject.
2. If paired supramaximal stimuli were delivered the amplitude of the second muscle action potential was lower than the first when the interval between the stimuli ranged from 16 m. secs. to 0.5 or 1.0 sec. (Fig. 5).
3. Repetitive nerve stimulation at frequencies as low as 5 per second caused an immediate reduction in the amplitude of the muscle action potentials followed by a return towards normal and then a more gradual expotential fall (Figs. 6 & 7).
4. Following a period of tetanic nerve

FIG. 5.—Paired stimuli at (i) half minute and (ii) minute intervals, showing the decreased amplitude of the second muscle action potential in the patient with myasthenia gravis (see legend opposite).

FIG. 6.—Repetitive nerve stimulation at 5 per second, showing an immediate reduction in the amplitude of the muscle action potentials followed by a temporary return to normal in the patient with myasthenia gravis (see legend opposite).

FIG. 7.—Repetitive nerve stimulation at 10 per second, showing the myasthenic decrement and the post-tetanic facilitation.

FIG. 5-7.—Electromyograms from a normal subject A, and a patient with myasthenia gravis B. Supramaximal stimuli to ulnar nerve and the action potentials recorded from the abductor digiti minimi by surface electrodes. Time trace 100 m. secs.

stimulation the response to a further stimulus after an interval of more than one second exceeded the amplitude of the initial stimulus (Fig. 7). This they termed post-tetanic facilitation; it was never seen in normal subjects.

The authors concluded that the type of neuromuscular block exhibited by patients with myasthenia gravis resembled that seen in the experimental animal as a result of partial curarisation. The molecule of curare bears a structural similarity to that of acetylcholine and thus competes for receptor sites at the membrane of the motor end-plate. It does not cause depolarisation of the membrane (Castillo and Katz, 1957) but it prevents the autogenous acetylcholine released from the nerve endings from finding a receptor site and in turn depolarising the motor end-plate. Unlike the block induced by curare, the myasthenic defect is progressively intensified by continuous nerve stimulation. Grob and his colleagues postulated that choline derived from the break-down of autogenous acetylcholine might be the blocking agent. The hypothesis of a circulating curare-like substance gains support from a paper by Walker (1938). She described how the muscles of the forearm were fatigued by exercise while the circulation was occluded with a tourniquet. The tourniquet was then released and the patient developed ptosis. This experiment was repeated by Wilson and Stoner (1944) with essentially similar results. Blood samples were also taken from the occluded arm before and after exercise. The serum was then applied to a frog nerve-muscle preparation and it was shown that a considerable degree of neuromuscular block developed. However, in this department we have been unable to reproduce the Walker effect and our failure has been shared by other authors (Nastuk, Straus and Osserman, 1959; Lammers and Most van Spijk, 1954).

The occurrence of neonatal myasthenia is still perhaps the best evidence of a humoral neuromuscular blocking agent.

Desmedt (1957) published results which were similar to those of Grob and others (1956), and compared the myasthenic defect with that obtained by the administration of hemicholinium (1958). Hemicholinium inhibits the synthesis of acetylcholine at the nerve ending and Desmedt reasoned that in myasthenia gravis the conduction block was due to a prejunctional failure of acetylcholine synthesis. However, the published evidence for such a hypothesis is inconclusive (Simpson, 1964b).

It has been suggested that there might be

a structural abnormality of the affected motor end-plates (Zaimis, 1953). This would raise the threshold for depolarisation and possibly bestow a peculiar affinity for the transmitter substance or its metabolite. This would account for the initial weakness and the progressively increasing neuromuscular block. The likelihood of a structural abnormality at the motor end-plate can be questioned on the grounds of the variability of the course of the disease with relatively sudden and complete remissions and relapses. There is the further evidence of neonatal myasthenia in which case the neuromuscular block is initially severe but resolves within a few weeks.

Simpson (1960) proposed the hypothesis of an auto-immune mechanism which would account for many of these apparently anomalous features. A circulating antibody if derived from the motor end-plate would presumably have a molecular structure which was similar to that of acetylcholine and would compete with it for the receptor sites. Furthermore, the antibody would have a specific life-span and thus dramatic changes in the clinical state would be accounted for. It might also pass the placental barrier and give rise to neonatal myasthenia gravis.

Independently Nastuk and others (1960) had found that the injection of serum from a patient with myasthenia gravis caused cytolysis in frog muscle. They, too, concluded that an auto-immune mechanism might be responsible. Strauss and others (1960) reported the presence of a muscle-binding, complement-fixing globulin in the serum of patients with myasthenia gravis. Beutner, Witebsky, Licken and Adler (1962) and Feltkamp, Geld, Kruffy and Oosterhuis (1963) confirmed these results, but paradoxically Simpson (1964a) reported a failure to show the specific changes with the immunofluorescence technique.

There are many discrepancies in these reports and it appears significant that positive results correlate with the presence of a thymoma. Strauss's report of muscle-binding globulin would be out of keeping with the fluctuating state of true myasthenia gravis and more like the severe and progressive form of the disease which is found accompanying a thymoma. As yet unrecognised antibodies with different organ specificities may well be present.

Diagnosis

The methods of diagnosis are threefold: clinical, pharmacological and electromyographic.

The Clinical Diagnosis

The essential criterion for a clinical diagnosis of myasthenia gravis is evidence of an abnormal degree of weakness developing during sustained or repeated muscular effort. The diagnosis may be suggested by the history, and the examination of the patient must be designed to test his response to exercise. Whenever possible an objective measurement should be made in preference to the examiner's subjective assessment.

(1) With the patient lying on the examination couch he is asked to raise his right leg and to keep it elevated for as long as possible. This is timed and the test is repeated with the left leg.

(2) He is asked to lift his head from the couch and to keep his neck flexed for as long as possible. This is timed.

(3) Sitting upright he is asked to raise his arms to the horizontal and to maintain this posture. This is timed for the right and left arm.

(4) The vital capacity should be estimated, either by spirometry or by asking the patient to count out loud during one breath after maximum inspiration. Normal individuals can count beyond 30 on one breath. Any fading of the voice is recorded. The strength of the cough is noted.

(5) The range of eye movements is assessed and the palpebral fissures are measured. The palpebral fissures are again measured after the patient has tried to maintain a maximum vertical gaze for one minute.

(6) The strength of jaw closure, jaw opening and eye closure are assessed.

While attempting to maintain the required posture, the limbs may fall apparently exhausted, only to recover strength a moment later. This may also affect the eyelids, causing a fluttering effect. This response should not be regarded as a hysterical manifestation, but may be accounted for by the phenomenon of post-tetanic facilitation (p. 361).

An accurate record of these results is essential, as it is only by comparison of muscular strength on different occasions and at different times of the day that the fluctuations of the disease can be recognised. This is especially important when the response to treatment is being assessed.

The Pharmacological Diagnosis

The diagnosis is not complete until it has been shown that the patient's muscular strength can be restored by the administration of anti-

cholinesterase drugs (Viets and Schwab, 1935).

Two anticholinesterase drugs, edrophonium chloride (Tensilon) and neostigmine methyl sulphate (Prostigmin) are routinely used in diagnosis.

Edrophonium (Osserman and Kaplan, 1952) acts rapidly and is thus very convenient for use in an outpatient department. The anticholinesterase effect is similarly shortlived so that any ill effects disappear within 5 minutes. In experienced hands it alone is often sufficient to establish the diagnosis, but I do not agree with Osserman (1958) who claimed that all the information required could be obtained with Tensilon. The very brevity of its effect allows the physician to examine only one or two muscle groups, so that the occurrence of permanent myopathic changes may give rise to a false negative interpretation.

Edrophonium (Tensilon) Test. Having made a baseline examination of the patient, 2 mg. (0.2 ml.) of edrophonium are given by intravenous injection. If there is no response within one minute a further 8 mg. (0.8 ml.) are injected. Non-myasthenic subjects show no improvement in their muscle strength and fasciculations are frequently seen in the orbicularis oculi, with watering of the eyes. The patient with myasthenia gravis shows an improvement in strength within one minute of the injection, and the occurrence of side effects is minimal (Fig. 3). The betterment usually persists for less than three minutes and a repeated examination after this time shows that the previous weakness has returned.

Neostigmine (Prostigmin) Test. The delayed onset and prolonged effect allow the examiner to make a more complete assessment than is possible during the edrophonium test. A baseline physical examination is made and 0.6 mg. atropine sulphate are given i.m. The patient is re-examined after 15 minutes. Any change can be discounted as a false positive response. 1-1.5 mg. neostigmine methyl sulphate is injected i.m. The effect is seen within 10 to 30 minutes. The duration of the effect is from 2 to 3 hours, and a complete physical and electromyographic evaluation can be made during this period. There should be an unequivocal objective improvement in the performance of the physical tests if a positive diagnosis of myasthenia gravis is to be made.

In rare instances it may be necessary to use one of the provocative tests. The patient with myasthenia gravis may be extremely sensitive to a small dose of curare. The curare sensitivity test is thus a dangerous procedure and should

not be undertaken unless there is serious doubt about the diagnosis and only if adequate measures for resuscitation including assisted respiration are available.

Curare Sensitivity Test. 3 mg. of d-tubocurarine per 18 kg. body weight is the intravenous curarising dose for a normal individual. The patient is given 2% of this dose. If no weakness develops within 5 minutes of the injection, 5% of the estimated dose is given (Bennet and Cash, 1943). A larger dose should not be used, as some otherwise normal subjects are made weak by as little as 10% of the usual curarising dose. The test seems even less valuable in light of a report of a normal resistance to curare shown by some patients with myasthenia gravis (Pelikan, Tether and Unna, 1953).

A similar sensitivity test utilising quinine bisulphate was described by Eaton (1943). It has the serious disadvantage that the weakness induced by quinine bisulphate, unlike that resulting from curarisation, is not reversible by anticholinesterase drugs.

The unusual tolerance of patients with myasthenia gravis to decamethonium iodide forms the basis for another diagnostic test (Churchill-Davidson and Richardson, 1952). The procedure is lengthy, requiring electromyographic control, and is seldom necessary in clinical practice.

The Electromyographic Diagnosis

Direct needle electromyography does not provide diagnostic evidence, and the electrophysiological diagnosis is based on the recorded response of the muscle to supramaximal nerve stimulation. The technique was described by Harvey and Masland (1941), and a summary of the findings in myasthenia gravis are listed on p. 361. These are taken from the extended account by Grob and others (1956). These tests may conveniently be combined with the pharmacological tests described in the previous section, thus providing objective evidence of the myasthenic phenomenon and its repair with anticholinesterase drugs.

Management

Drug treatment

Neostigmine (Prostigmin) bromide, 15 mg./tablet.

Pyridostigmine (Mestinon) bromide, 60 mg./tablet.

The management of the patient with myasthenia gravis has been likened to the management of the diabetic (Johns, 1960). In both

conditions an adequate control of symptoms can be achieved in most cases with the appropriate drugs. The underlying disease is seldom cured and the fluctuations in its severity necessitate frequent reappraisal of the drug requirements. There is no standard dose of medication, but the appropriate dose must be determined for the individual. Overdosage gives rise to a clinical picture which to the inexperienced observer may be confused with underdosage.

Although there is still controversy regarding the site of action of the anticholinesterase drugs, it is generally agreed that they increase the effectiveness of autogenous acetylcholine at the neuromuscular junction. This is the nicotinic effect. They also have a muscarinic effect, stimulating smooth muscle and increasing glandular secretion. These are regarded as side effects, and include excessive bowel action with borborygmi, colic and diarrhoea; sweating; hypersalivation and excessive production of tears and bronchial secretions; and constriction of the pupils. Patients with myasthenia gravis develop a tolerance to the muscarinic effects more readily than normal individuals.

The ideal dosage of anticholinesterase drugs increases the strength of the initial muscular effort, and defers the development of weakness ("fatigue"). An excessive dose gives rise to an increase in muscle weakness and fasciculation due to the persistence of acetyl choline at the neuromuscular junction—"depolarisation" or cholinergic block.

As the severity of the myasthenic defect varies in different muscle groups, so will their drug requirements differ. If one group of muscles is ideally dosed, others will show overdosage while some remain underdosed. One must often accept a relative underdosage in some parts of the body if essential muscles, such as the respiratory muscles, are not to be overdosed.

The exact timing of doses varies according to the patient's routine, e.g. meal times, etc. In general the interval between doses should be 4 to 5 hours, the approximate duration of drug action. Some patients require more frequent doses and others less frequent. I prefer that there should be a slight "let-down" of effect at the end of a dose period, with a consequent resurgence of strength when the next dose takes effect. This allows both the patient and the physician to recognise any fluctuations in the severity of the disease and the drug requirements.

The choice between neostigmine and pyridostigmine

stigmine largely depends upon the response of the patient. The duration of effect is roughly equal, although neostigmine seems to reach its peak activity a little sooner than pyridostigmine, which has the reputation for a "smoother" effect. Some physicians use neostigmine during the day, giving the patients pyridostigmine on retiring. This often obviates the necessity for waking for a dose during the night.

For a patient with mild to moderately severe myasthenia gravis, a suitable trial regime would be, one tablet of neostigmine (15 mg.) at 7.30 a.m., 11.30 a.m., 3.30 a.m., 7 p.m. and 11 p.m. The patient should be examined at hourly intervals through the day according to the method described in the previous section. This should indicate the degree of response to each dose, and the size of the individual doses can then be varied until the optimum response is obtained. Side effects can be controlled with atropine sulphate 0.6 mg. orally or by intramuscular injection, remembering that atropine may mask an increase in side effects which heralds overdosage. The ease with which the disease can be controlled varies from patient to patient; like diabetics, some patients with myasthenia gravis are notoriously "brittle" and should be reviewed at frequent intervals.

Pyridostigmine, 60 mg., can be introduced in place of the neostigmine. The rate of excretion of anticholinesterase drugs varies from patient to patient and some patients show a tendency to accumulate pyridostigmine. For this reason we do not use the longer acting anticholinesterase drugs such as bis-neostigmine, bis-pyridostigmine and ambenonium chloride (Mytelase).

Cholinergic crisis

Sudden worsening in a previously well-controlled patient, particularly if there seems to be a "resistance to drugs" is most often due to overdosage. If the situation is not life-threatening, the patient should be rested in bed and the previously effective drug regime continued. Hourly observations of muscle strength and the occurrence of side-effects should be instituted. It should be apparent after the first one or two doses if the weakness increases after each dose. The edrophonium test is a useful adjunct to the diagnosis of cholinergic crisis. One to one-and-a-half hours after the routine medication an edrophonium test is performed. If there is a prompt improvement in strength, the patient is underdosed. If the response is equivocal or if there is an increase in the weakness then the

patient is overdosed. Edrophonium normally has a very rapid and brief action so that any worsening is short-lived. However, it has been postulated that it also has a direct effect on the motor end-plate membrane so that at critical levels of overdosage it may induce a persistent "depolarisation" block (Tether, 1951; Osserman and Kaplan, 1952; Westerberg, Magee and Shideman, 1953). If unexpected, this response might be fatal.

In more severe cases, when weakness has proceeded to collapse, all anticholinesterase medication should be withdrawn and the patient given atropine sulphate 2 mg. i.m. The ventilatory capacity should be estimated and if necessary, artificial respiration instituted. Mouth-to-mouth resuscitation may be life-saving. An airway must be maintained, preferably with an endotracheal tube so that a mechanical respirator can be used. A tracheostomy should be performed if it appears that assisted respiration will be required for more than a few hours. Bronchorrhoea is a common complication of the cholinergic state and the tracheostomy will facilitate bronchial toilet.

Further anticholinesterase medication should be withheld until there is an unequivocally positive response to edrophonium. The period without drugs may extend for as long as 4 days.

The oximes, pyridine-2-aldoxime (2 PAM), its methane sulphonate (P_2S) and diacetyl monoxime (DAM) have been shown to reactivate cholinesterase which was inhibited by organo-phosphates (Wilson and Ginsburg, 1955; Childs and others, 1955). Grob and Johns (1958 a & b) showed a reversal of the anticholinesterase effect of neostigmine. In this department PAM and P_2S have been used in the emergency treatment of cholinergic crisis. In the recommended dosage the clinical effect was slight and delayed by more than 30 minutes. Used in this way, they are of little practical value.

Ancillary drug treatment

The patient with myasthenia gravis may develop hypokalaemia due to diarrhoea, and may respond favourably to potassium supplements, e.g. potassium bicarbonate 1 gm. q.i.d. Desmedt (1945) suggested that potassium actually supplemented the effect of neostigmine. Ephedrine, 25 mg. t.d.s., introduced by Edgeworth in 1930, is still used. It is thought to act by inhibiting amine oxidase and so to potentiate the action of adrenaline. It is difficult to show any measurable effect.

Thymectomy

The value of thymectomy in the treatment of myasthenia gravis is still the subject of controversy. Blalock, who was responsible for the re-introduction of this form of treatment, (Blalock, Harvey, Ford and Lilienthal, 1941), and the other workers from the Johns Hopkins Hospital, became increasingly dissatisfied with their results (Blalock, 1944; Harvey, 1948; Grob, 1953). Keynes had a quite different impression (Keynes, 1946, 1949, 1953, 1954, 1955), stressing the necessity for a discriminating selection of suitable patients for the operation.

Patients with a tumour of the thymus or myopathic changes in the muscles in general responded poorly. Simpson published a comprehensive evaluation of Keynes' cases (Simpson, 1958) which in general confirmed Keynes' earlier reports. He concluded that the apparent discrepancies between his results and those of the Americans (Blalock, 1944; Harvey, 1948; Eaton and colleagues, 1949, 1950, 1953; Schwab and Leland, 1953) were due to different methods of analysis and different criteria for improvement. Simpson found that young women with a history of myasthenia gravis of less than five years most consistently benefitted from operation. Some men and some older patients who had a longer history of the disease also showed marked improvement. Viets and Schwab (1961) reviewing their cases in the light of this paper corroborated Simpson's results. Simpson (1964) currently recommends thymectomy to all patients under the age of 50 years with a history of generalised myasthenia gravis of not more than five years' duration.

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